Solvent-Free Synthesis of Racemic α-Amino Nitriles

Alejandro Baeza, Carmen Nájera,* and José M. Sansano

Departamento de Química Orgánica and Instituto de Síntesis Orgánica (ISO). Facultad de Ciencias

Universidad de Alicante, Apdo. 99, 03080-Alicante (Spain).

Fax: +34-965903549. E-mail: cnajera@ua.es.

Abstract: A very simple one-step environmentally friendly procedure for the synthesis of α-amino nitriles from aldehydes and ketones, using TMSCN in absence of solvent, is reported. The active catalyst of this three-component (Strecker) reaction was the own amine employed in the transformation. In general, aldehydes react more rapidly than ketones and gave almost quantitative yields of the corresponding α-amino nitriles in less than fifteen minutes. Only cyclic ketones afford excellent chemical yields under these conditions.

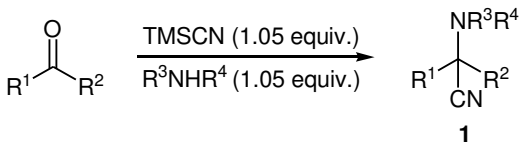
Key words: addition reactions, Strecker synthesis, catalysis, amino-nitriles, green chemistry, solvent-free.

The Strecker reaction, which allows the synthesis of α-amino nitriles, was discovered in 1850,[1] being the first multicomponent reaction reported.[2] The advantages of the Strecker-type reactions have attracted many chemists to focus on the design of suitable asymmetric and non racemic versions of this efficient α-amino acid (α-AA) synthesis.[3] One of the most remarkable features of this process is the easy accessibility to very important proteinogenic and non-proteinogenic α-amino acid derivatives, especially arylglycines, which are very difficult to obtain by other preparative methods. In addition, the resulting α-amino nitriles, proposed as prebiotic precursors to porphyrins, corrins nicotinic and nucleic acids by Eschenmoser,[3b] have been employed as precursors of iminium ions in the synthesis of natural products and heterocyclic compounds. The corresponding α-metallated α-amino nitriles (masked acyl anion equivalent) have been used in the generation of multiple polyfunctional structures as diamines, aminoalcohols enamines, carbonyl compounds, etc.[3]

Although enantioselective processes were unknown till the middle of the 1990s, the popular synthesis of racemic α-amino nitriles is very well known. It is usually based on the use of performed imines and subsequent addition of HCN, TMSCN or another cyanide source, in the presence of a catalyst, although direct processes are also known. These last ones represent a more attractive route than the sequential reactions, and all the efforts have been focused to develop easier methods to obtain these α-amino nitriles. Numerous examples has been reported in the last years, being, in all the cases, necessary the use of catalyst to achieve successful results, such as Lewis acid, for example, $La(OPr^i)_3$, $Sc(OTf)_3$, $BiCl_3$, $NiCl_2$, $RuCl_3$, $Cu(OTf)_2$, sulfonium salts,[4] Lewis bases like Et_3N,[4f] and even montmorillonite KSF[5] or iodine.[6] To the best of our knowledge there are only two processes where the presence of the catalyst could be avoided. In both cases the presence of the solvent becomes crucial, acting as catalyst.[7]

On the other hand, the absence of solvent in this organic synthesis makes the procedure simpler, saves energy and prevents solvent wastes, hazards and toxicity. In this sense a solvent-free synthesis of α-amino nitriles employing excesses of the carbonyl compound (aldehyde or ketone) was reported in 1985.[8] This reaction cannot be considered as a one pot process because the imine was formed previously by heating the reaction mixture at 100 ºC, and then an excess of the TMSCN was required to obtain the desired nitriles after heating at 100 ºC. Most recently, it has been reported the first effective three component Strecker reaction in absence of solvents, however, the presence of magnesium bromide-ethyl etherate as Lewis acid catalyst was also necessary.[9] Continuing our research in the solvent-free organic synthesis and based on the experience in an analogous reaction for obtaining *O*-protected cyanohydrins,[10] here we reported the three-component Strecker reaction in the absence of solvents and catalysts, avoiding waste reagents an work-up protocols.

The initial reaction was performed with freshly distilled benzaldehyde, aniline (1.05 equiv.) and TMSCN (1.05 equiv.). The amino nitrile **1a** was obtained quantitatively after 3 min as crude pure compound (Table 1, entry 1). Easily removable amino groups as 4-methoxyphenyl (PMP) and benzyl were next introduced from the corresponding amine, obtaining amino nitriles **1b** and **1c**, respectively, in excellent yields and purity and in very short reaction times (Table 1, entries 2 and 3). The same reaction occurred when allylamine was used, giving quantitatively product **1d** in only 3 min (Table 1, entry 4). The use of symmetrically or usymmetrically substituted secondary amines led to a slight increase on the reaction time (Table 1, entries 6-8) without any detriment of the chemical yield.



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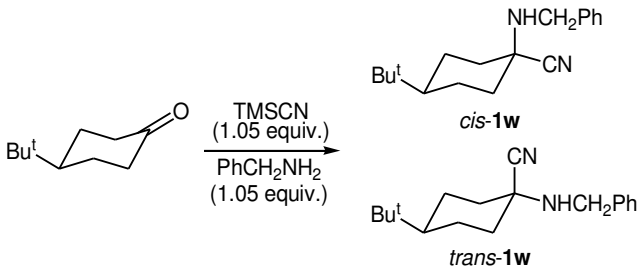
Scheme 1. Synthesis of α-amino nitriles **1**

When 4-chlorobenzaldehyde, isobutyraldehyde, dihydrocinnamaldehyde and α,β-unsaturated aldehydes, such as (*E*)-cinnamaldehyde and (*E*)-octenal were allowed to react with primary amines the corresponding α-amino nitriles were obtained in high yields in short reaction times, independently of the amine employed. (Table 1,

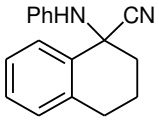
entries 9-15 and 17). Lower yield and higher reaction time was observed when the secondary amine dibenzylamine reacted with isobutyraldehyde (Table 1, entry 16). In this example, the mixture of the amine and the aldehyde was kept during 5 min previously to the addition of the cyanide source in order to minimize the large amount of cyanohydrin obtained when all the reagents were put together. Compound **1p** only could be isolated in 74% yield, perhaps the imine was not formed as fast as it was expected due to the steric repulsion between the bulky dibenzylamine and the α-branched aldehyde (Table 1, entry 16).

Ketones reacted very slowly with benzylamine and the reaction was incomplete spite to maintain higher reaction times. Particularly, acetophenone gave very poor yield of nitrile **1r** (Table 1, entry 18), and α,β-unsaturated ketones failed under these reaction conditions. In the case of methyl vinyl ketone (Table 1, entry 19) Michael type addition products of the amine onto the conjugated system and unidentified products were detected by ^{1}H NMR of the crude material. In contrast when benzylideneacetone was used, cyanohydrin product was obtained as major product (Table 1, entry 20). Non-aromatic cyclic and cyclic aliphatic ketones are more appropriate substrates for this solvent-free Strecker reaction, thus 3-pentanone gave the desired nitrile **1u** in 77% pure yield (Table 1, entry 21) and the corresponding cyanohydrin in 23% yield. Cyclopentanone and 4-*tert*-butylcyclohexanone gave excellent yields of **1v** and **1w**, respectively in 12-13 min (Table 1, entries 22 and 23). Heterocyclic aliphatic ketones, such as tetrahydropyran-4-one and tetrahydrothiopyran-4-one, were also tested giving the corresponding Strecker adducts **1x** and **1y** in excellent yields and in short reaction times (Table 1, entries 24 and 25). All of the reactive ketones depicted on Table 1 (entries 21-25) reacted with 1.2 equiv of TMSCN and 1.3 equiv of benzylamine and always stirring during 5 min the mixture aldehyde/benzylamine before adding the TMSCN, except for the 4-*tert*-butylcyclohexanone, which reacted under the same reaction conditions as followed for the aldehydes. In this case, the product **1w** was obtained as a >95/5 *cis/trans* mixture of diastereoisomers by the chemical shifts and NMR experiments (NOESY) (Scheme 2).



Scheme 2. Synthesis of the α-amino nitriles derived from 4-*tert*-butylcyclohexanone.

As occurred in the reaction using aromatic ketones, benzocondensed cyclic ketones, like indanone and α-tetralone, gave cyanohydrins exclusively under the reaction conditions described before. For these unsuccessful examples we decided to use the conditions where a sequential reaction took place after mixing the ketone and the amine at 100 ºC for 1 min followed by reaction of the resulting mixture with TMSCN at 100 ºC for 15 min.[8] Thus, actetophenone gave a 71% of the product **1r**, meanwhile α-tetralone afforded α-amino nitrile **1z** in 69% yield (both of them obtained after column chromatography).



1z

In order to avoid the use of hazardous TMSCN, we thought about the possibility to replace it for acetone cyanohydrin (1.05 equiv.), in the reaction of benzaldehyde and benzylamine (1.05 equiv.). Under this new reaction conditions the corresponding α-amino nitrile **1a** was obtained after 20 min in a 91% of conversion (determined by ^{1}H NMR), unfortunately the reaction crude was not very clean and even some unidentified products were observed.

Other cyanide sources as diethyl cyanophosphonate, methyl cyanoformate or benzoyl cyanide were also tested, instead of TMSCN as cyanide source, in the Strecker type reaction of benzaldehyde and benzylamine. In these reactions it was not obtained neither α-amino nitrile (free base or *N*-protected) nor cyanohydrin product. Presumably a large amount of amine reacts with the cyanide source, causing total decomposition, which was observed by ^{1}H NMR and ^{13}C NMR analysis. The addition of KCN onto benzaldehyde in presence of ammonium chloride or ammonium hydroxide to achieve the corresponding free α-amino nitrile was also essayed leading in both cases to a complex mixture of products as occurred under the published reaction conditions.[8]

The presence of HCN in commercial TMSCN, as we have already demonstrated by ^{13}C NMR in previous works,[10,11] seems to be crucial in reaction pathway since it could activate the carbonyl compound, acting as Brönsted acid, favoring the imine formation. This affirmation was supported by two simultaneous ^{1}H NMR experiments. In one of them equimolecular amounts of benzaldehyde and benzylamine were mixed, and in other experiment the same components and TMSCN were allowed to react. In the first experiment, it was observed that the imine formation took place instantaneously. It was also detected –through the second experiment- that the α-amino nitrile was obtained faster than the imine formation (less than 10 min respectively) showing the role of HCN as acidic catalyst to imine formation. It is noteworthy that in the second experiment a little proportion of cyanohydrin compound was detected as consequence of the dilution, which makes slower the process, favoring the irreversible side reaction. Also important result was the previous fast formation of the imine and further attack of the cyanide anion, otherwise cyanohydrin would be obtained as major reaction product. In addition, the amine (placed in very slight excess) could activate HCN, by formation of ammonium salt, and increasing the reaction rate.[10] By other side the high proportion of cyanohydrin, obtained in some cases, could be explained because the amine itself catalyzes the process, [10] which is favored when the imine formation becomes slow as it is described above.

In accordance with this observations and the reactivity observed we can conclude that a new methodology for the synthesis of α-amino nitriles from aldehydes and aliphatic ketones has been developed. This environmental friendly one-pot reaction proceeded at room temperature, without solvent, with the minimum amounts of reagents avoiding the typical work-up. The crude reaction product did not require any further purification. This procedure, which reduces the amount of the cyanide reagents to the minimum and proceeds under mild conditions without the presence of catalyst, is prone to be applied to an industrial level.

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Experimental.

General Procedure for the synthesis of α-amino nitriles:
The corresponding amine (1.05 eq., 0.525 mmol) and trimethylsilylcyanide (1.05 eq., 0.525 mmol) were added subsequently onto the carbonyl compound (1 eq. 0.5 mmol) (in some cases, indicated in Table 1, the amine and the carbonyl compound were let to react five minutes before the TMSCN addition). Then the mixture was stirred until the reaction was judged to complete. The mixture was evaporated to remove the little excess of TMSCN (Caution! Hazardous compound!) and the final pure α-amino nitriles were obtained either by distillation or by crystallization in hexanes. Only when crude yields are lower than 90% purification by flash chromatography was necessary to afford the pure compounds (see Table 1). Spectroscopic and physical data for new compounds **1** follows.

2-Phenyl-2-(phenylamino)acetonitrile (1a)[5]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.12 (br. s, 1H, NH), 5.42 (s, 1H, CHCN), 6.77 (d, *J* = 8.0 Hz, 2H, ArH), 6.89 (t, *J* = 7.4 Hz, 1H, ArH), 7.27 (t, *J* = 7.8 Hz, 2H, ArH), 7.45 (m, 3H, ArH), 7.60 (m, 2H, ArH).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 50.1 (*C*HCN), 114.1 (CN), 118.2, 120.8, 127.2, 129.2, 129.4, 129.5, 134.0, 144.6 (ArC).

2-(4-Methoxybenzylamino)-2-phenylacetonitrile (1b)[12]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.24 (br. s, 1H, NH), 3.81 (s, 3H, OCH_3), 3.90 and 4.00 (2xd , *J* = 13.1 Hz, 2H, CH_2Ph), 4.73 (s, 1H, CHCN), 5.19 (dd, *J* = 1.5, 10.2 Hz, 1H, CH=CH_{2Z}), 5.19 (dd, *J* = 1.5, 17.2 Hz, 1H, CH=CH_{2E}), 5.90 (m, 1H, C*H*=CH_2), 7.37-7.43 (m, 3H, ArH), 7.39 (m, 3H, ArH), 7.52 (m, 2H, ArH).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 50.7 (*C*HCN), 53.2 (CH_2Ph), 55.3 (OCH_3), 118.7 (CN), 114.0, 127.3, 128.9, 129.0, 129.7, 130.1, 134.8, 159.1 (ArC).

2-(Benzylamino)-2-phenylacetonitrile (1c)[5]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.21 (br. s, 1H, NH), 3.92 and 4.03 (2xd, *J* = 13.1 Hz, 2H, CH_2Ph), 4.72 (s, 1H, CHCN), 6.77 (d, *J* = 8.0 Hz, 2H, ArH), 7.15 (m, 1H, ArH), 7.22-7.41 (m, 6H, ArH), 7.51 (m, 2H, ArH).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.2 (*C*HCN), 53.4 (CH_2Ph), 118.7 (CN), 127.2, 127.6, 128.3, 128.6, 128.9, 129.0, 134.7, 138.1 (ArC).

2-(Allylamino)-2-phenylacetonitrile (1d)[13]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.46 (br. s, 1H, NH), 3.41 and 3.49 (2xm, 2x1H, CH_2NH), 4.79 (s, 1H, CHCN), 6.77 (d, *J* = 8.0 Hz, 2H, ArH), 7.15 (m, 1H, ArH), 7.22-7.41 (m, 6H, ArH), 7.51 (m, 2H, ArH).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 49.8 (CH_2NH), 53.4 (*C*HCN), 117.8 (CH_2=CH), 118.7 (CN), 127.2, 128.9, 129.0, 134.7 (ArC), 134.7 (CH_2=*C*H).

2-(Benzhydrylamino)-2-phenylacetonitrile (1e)[14]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.71 (br. s, 1H, NH), 4.59 (s, 1H, CHCN), 5.24 (s, 1H, $CHPh_2$), 7.21-7.58 (m, 15H, ArH).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.4 (*C*HCN), 59.5 ($CHPh_2$), 118.7 (CN), 126.9, 127.1, 127.2, 127.4, 127.9, 128.5, 128.7, 128.9, 129.0, 134.9, 141.1, 142.7 (ArC).

2-(Dibenzylamino)-2-phenylacetonitrile (1f)[4a]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.41 and 3.87 (2xd , *J* = 13.4 Hz, 2x2H, 2xCH_2Ph), 4.90 (s, 1H, CHCN), 7.25-7.42 (m, 13H, ArH), 7.57 (d, *J* = 7.5 Hz, 2H, ArH).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 54.9 (CH_2Ph), 57.3 (*C*HCN), 115.4 (CN), 127.7, 128.6, 128.7, 128.8, 128.8, 128.9, 133.9, 137.7 (ArC).

2-(*N*-Benzyl-*N*-methylamino)-2-phenylacetonitrile (1g)[4a]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.25 (s, 3H, CH_3), 3.54 and 3.81 (2xd, *J* = 13.1 Hz, 2x1H, CH_2Ph), 4.87 (s, 1H, CHCN), 7.28-7.41 (m, 8H, ArH), 7.53 (d, *J* = 7.5 Hz, 2H, ArH).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 38.2 (CH_3), 59.2 (CH_2Ph), 60.1 (*C*HCN), 115.1 (CN), 127.6, 127.7, 128.5, 128.6, 128.7, 128.8, 133.7, 137.4 (ArC).

2-Phenyl-2-(pyrrolidin-1-yl)acetonitrile (1h)[4g]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.81 (br. m, 4H, 2xCH_2), 2.62 (br. m, 4H, 2xCH_2), 5.03 (s, 1H, CHCN), 7.33-7.41 (m, 3H, ArH), 7.49-7.52 (m, 2H, ArH).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.3 (2xCH_2), 50.1 (2xCH_2N), 59.2 (*C*HCN), 116.0 (CN), 127.5, 128.6, 128.9, 134.1 (ArC).

2-(Benzylamino)-2-(4-chlorophenyl)acetonitrile (1i)[7b]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.18 (br. s, 1H, NH), 3.92 and 4.02 (2xd, *J* = 13.0 Hz, 2x1H, CH_2Ph), 4.71 (s, 1H, CHCN), 7.24-7.39 (m, 8H, ArH), 7.47 (d, *J* = 9.6 Hz, 2H, ArH).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.1 (*C*HCN), 52.7 (CH_2Ph), 118.3 (CN), 127.1, 127.7, 128.3, 128.5, 128.6, 129.0, 133.2, 137.8 (ArC).

(*E*)-4-Phenyl-2-(phenylamino)but-3-enenitrile (1j)[5]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.91 (br. s, 1H, NH), 5.04 (br. s, 1H, CHCN), 6.24 (dd, *J* = 5.2, 16.0 Hz, 1H, C*H*CHCN), 6.77 (d, *J* = 7.8 Hz, 2H, ArH), 6.90 (t, *J* = 7.4 Hz, 1H, ArH), 7.03 (d, *J* = 16.0 Hz, 1H, PhCH), 7.25-7.44 (m, 7H, ArH).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 47.7 (*C*HCN), 117.7 (CN), 120.4 (*C*HCHCN), 114.4, 121.0, 127.0, 128.8, 128.9, 129.6, 134.9, 144.4 (ArC), 135.1 (Ph*C*H).

(*E*)-2-(Benzylamino)-4-phenylbut-3-enenitrile (1k)[15]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.97 (br. s, 1H, NH), 3.90 and 4.07 (2xd, *J* = 13.1 Hz, 2x1H, CH_2Ph), 4.37 (d, *J* = 5.2 Hz, 1H, CHCN), 6.17 (dd, *J* = 5.2, 15.9 Hz, 1H, C*H*CHCN), 6.91 (d, *J* = 15.9 Hz, 1H, PhCH), 7.24-7.40 (m, 10H, ArH).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.1 (*C*HCN), 51.2 (CH_2Ph), 118.2 (CN), 122.4 (*C*HCHCN), 126.8, 127.6, 128.4, 128.5, 128.6, 128.7, 135.2, 138.1 (ArC), 134.1 (Ph*C*H).

(*E*)-2-(Dibenzylamino)-4-phenylbut-3-enenitrile (1l)[4a]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.42 and 4.01 (2xd, *J* = 13.5 Hz, 2x2H, 2xCH_2Ph), 4.50 (d, *J* = 2.4 Hz, 1H, CHCN), 6.08 (dd, *J* = 4.4, 16.1 Hz, 1H, C*H*CHCN), 6.93 (d, *J* = 16.1 Hz, 1H, PhCH), 7.24-7.41 (m, 15H, ArH).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.3 (CH_2Ph), 77.2 (*C*HCN), 115.4 (CN), 122.7 (*C*HCHCN), 126.8, 127.6, 128.5, 128.6, 128.7, 128.8, 135.3, 137.8 (ArC), 134.7 (Ph*C*H).

(*E*)-2-(Benzylamino)non-3-enenitrile (1m)

Yellow sticky oil.
TLC: R_f 0.68 (*n*-hexane/ethyl acetate:4/1).
IR (KBr): 3327, 2254, 1653, 1454, 1381 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.7 Hz, 3H, CH_3), 1.24-1.41 (m, 6H, 3xCH_2), 2.07 (m, 2H, CH_2CH), 3.01 (br. s, 1H, NH), 3.83 and 3.99 (2xd, *J* = 12.9 Hz, 2x1H, CH_2Ph), 4.15 (d, *J* = 5.2 Hz, 1H, CHCN), 5.50 (dd, *J* = 5.2, 15.5 Hz, 1H, C*H*CHCN), 6.04 (m, 1H, C*H*=CHCHCN), 7.26-7.37 (m, 5H, ArH).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (CH_3), 22.4, 28.3, 31.2, 31.9 (4xCH_2), 46.0 (*C*HCN), 51.0 (CH_2Ph), 118.5 (CN), 123.1 (*C*HCHCN), 127.5, 128.3, 128.5, 138.2 (ArC), 136.2 (*C*H=CHCHCN).
MS (EI): *m/z* = 215 (M^+ - HCN, 5%), 202 (19), 188 (65), 175 (21), 160 (32), 132 (31), 131 (22), 130 (27), 118 (59), 117 (54), 107 (19), 106 (27), 92 (24), 91 (100).
HRMS: *m/z* calcd for $C_{16}H_{22}N_2$: 242.1783; found: 242.1777.

3-Methyl-2-(phenylamino)butanenitrile (1n)[7a]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16 and 1.19 (2xd, *J* = 6.7 Hz, 2x3H, 2xCH_3), 2.10-2.21 (m, 1H, C*H*CH_3), 3.79 (br. s, 1H, NH), 4.03 (d, *J* = 5.6 Hz, 1H, CHCN), 6.71 (dd, *J* = 0.9, 7.8 Hz, 2H, ArH), 6.86 (dt, *J* = 0.9, 7.4 Hz, 1H, ArH), 7.24 (dt, *J* = 0.9, 7.4 Hz, 2H, ArH).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.2 and 19.1 (2xCH_3), 31.6 (*C*HCH_3), 52.5 (*C*HCN), 118.7 (CN), 114.0, 119.9, 129.5, 145.1 (ArC).

2-(Benzylamino)-3-methylbutanenitrile (1o)[7b]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 and 1.09 (2xd, *J* = 3.0 Hz, 2x3H, 2xCH_3), 1.94-2.06 (m, 2H, C*H*CH_3+NH), 3.29 (d, *J* = 5.9 Hz, 1H, CHCN), 3.81 and 4.08 (2xd, *J* = 13.1 Hz, 2x1H, CH_2Ph), 7.25-7.38 (m, 5H, ArH).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.2 and 19.2 (2xCH_3), 31.5 (*C*HCH_3), 51.8 (CH_2), 56.3 (*C*HCN), 119.4 (CN), 127.5, 128.3, 128.5, 138.4 (ArC).

2-(Dibenzylamino)-3-methylbutanenitrile (1p)[16]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.01 and 1.03 (2xd, *J* = 6.9 Hz, 2x3H, 2xCH_3), 1.95 (m, 1H, C*H*CH_3), 3.81 (s, 2x2H, 2xCH_2Ph), 4.15 (d, *J* = 5.8 Hz, 1H, CHCN), 7.25-7.36 (m, 10H, ArH).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.5 and 17.6 (2xCH_3), 33.8 (*C*HCH_3), 53.1 (2xCH_2), 55.4 (*C*HCN), 119.3 (CN), 126.9, 128.3, 128.6, 137.8 (ArC).

2-(Dibenzylamino)-4-phenylbutanenitrile (1q)

Colourless sticky oil.
TLC: R_f 0.53 (*n*-hexane/ethyl acetate:4/1).
IR (KBr): 3318, 2225, 1736, 1496, 1454, 1244 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.66 (br. s, 1H, NH), 2.06 (q, *J* = 7.6 Hz, 2H, CH_2CH), 2.82 (m, 2H, CH_2CH_2Ph), 3.45 (t, *J* = 7.2 Hz, 1H, CHCN), 3.78 and 4.04 (2xd, *J* = 12.5 Hz 2x1H, HN-CH_2Ph), 7.13-7.33 (m, 10H, ArH).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.6 (CH_2CH_2Ph), 35.0 (*C*H_2CH), 48.8 (*C*HCN), 51.6 (HN-*C*H_2Ph), 120.1 (CN), 126.3, 127.5, 128.3, 128.4, 128.5, 128.6, 138.3, 139.9 (ArC).
MS (EI): *m/z* = 223 (M^+ - HCN, 36%), 132 (77), 105 (19), 91 (100).
HRMS: *m/z* calcd for $C_{16}H_{17}N$ (M^+ - HCN): 223.1361; found: 243.1355.

2-(Benzylamino)-2-ethylbutanenitrile (1u)[17]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.03 and 1.04 (2xt, *J* = 7.4 Hz, 2x3H, 2xCH_3), 1.65 (br. s, 1H, NH), 1.72-1.85 (m, 2H, C*H*CH_3), 3.86 (s, 2H, CH_2Ph), 7.28-7.39 (m, 5H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.7 (CH_3), 28.9 (CH_2), 48.9 (*C*H_2Ph), 60.4 (*C*CN), 119.1 (CN), 127.4, 128.3, 128.6, 139.3 (ArC).

1-(Benzylamino)cyclopentanecarbonitrile (1v)
White solid; mp: 43-44 ºC (hexane).
TLC: R_f 0.59 (*n*-hexane/ethyl acetate:4/1).
IR (KBr): 3316, 2219, 1496, 1454 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.64 (br. s, 1H, NH), 1.81-1.90 (m, 6H, CH_2), 2.08-2.17 (m, 2H, CH_2), 3.88 (s, 2H, CH_2Ph), 7.25-7.37 (m, 5H, ArH).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.5 and 38.9 (2xCH_2), 50.1 (*C*H_2Ph), 61.2 (*C*CN), 122.9 (CN), 127.3, 128.3, 128.5, 139.2 (ArC).
MS (EI): *m/z* = 173 (M^+ - HCN, 41%), 172 (19), 91 (100).
HRMS: *m/z* calcd for $C_{12}H_{15}N$ (M^+ - HCN): 173.1204; found: 173.1199.

1-(Benzylamino)-4-tert-butylcyclohexanecarbonitrile (1w)
Colourless prisms; mp: 81-82 ºC (hexane).
TLC: R_f 0.70 (*n*-hexane/ethyl acetate:4/1).
IR (KBr): 3316, 2252, 1479, 1467, 1454 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 [s, 9H, C(CH_3)$_3$], 1.25-1.47 (m, 4H, CH_2), 1.52-1.63 (br. m, 2H, CH + NH), 1.83 and 2.16 (2xm, 2x2H, CH_2), 3.93 (s, 2H, CH_2Ph), 7.29-7.38 (m, 5H, ArH).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.8 (CH_2), 27.5 [C(*C*H_3)$_3$], 32.3 [*C*(CH_3)$_3$], 36.7 (CH_2), 47.3 (CH), 48.8 (*C*H_2Ph), 58.1 (*C*CN), 122.0 (CN), 127.4, 128.4, 128.6, 139.4 (ArC).
MS (EI): *m/z* = 243 (M^+ - HCN, 26%), 228 (48), 186 (18), 158 (18), 91 (100).
HRMS: *m/z* calcd for $C_{17}H_{25}N$ (M^+ - HCN): 243.1987; found: 243.1986.

4-(Benzylamino)-tetrahydro-2*H*-pyran-4-carbonitrile (1x)

White solid; mp: 71-73 ºC (hexane).
TLC: R_f 0.22 (*n*-hexane/ethyl acetate:4/1).
IR (KBr): 3302, 2221, 1477, 1449, 1431 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.60 (br. s, 1H, NH), 1.83 and 2.04 (2xm, 2x2H, 2xCH_2CCN), 3.70 and 3.99 (2xm, 2x2H, 2xCH_2O), 3.93 (s, 2H, CH_2NH), 7.26-7.40 (m, 5H, ArH).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.9 (*C*H_2CCN), 48.3 (CH_2NH), 55.0 (*C*CN), 63.8 (CH_2O), 121.1 (CN), 127.5, 128.3, 128.6, 138.8 (ArC).
MS (DIP-EI): *m/z* = 216 (M^+ , 5%), 157 (9), 106 (14), 91 (100).
HRMS: *m/z* calcd for $C_{12}H_{15}NO$ (M^+ - HCN): 189.1154; found: 189.1126.

4-(Benzylamino)-tetrahydro-2H-thiopyran-4-carbonitrile (1y)

Colourless prisms; mp: 76-77 ºC (hexane).
TLC: R_f 0.38 (*n*-hexane/ethyl acetate:4/1).
IR (KBr): 3309, 2217, 1475, 1453, 1429 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.71 (br. s, 1H, NH), 1.98 and 2.34 (2xm, 2x2H, 2xCH_2CCN), 2.81 (m, 4H, 2xCH_2O), 3.91 (s, 2H, CH_2NH), 7.26-7.39 (m, 5H, ArH).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.2 (CH_2S), 36.7 (*C*H_2CCN), 48.2 (CH_2NH), 56.7 (*C*CN), 121.0 (CN), 127.5, 128.3, 128.6, 138.8 (ArC).
MS (EI): *m/z* = 205 (M^+ - HCN, 23%), 177 (17), 91 (100).
HRMS: *m/z* calcd for $C_{12}H_{15}NS$ (M^+ - HCN): 205.0925; found: 205.0951.

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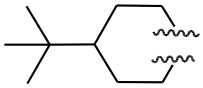
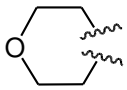
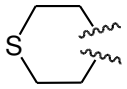
Table 1. Synthesis of racemic α-amino nitriles **1**.

Entry	R^1	R^2	R^3	R^4	t (min)	**1**	Yield (%)[a]
1	Ph	H	Ph	H	3	**1a**	99
2	Ph	H	4-MeO-C_6H_4	H	7	**1b**	99
3	Ph	H	$PhCH_2$	H	3	**1c**	99
4	Ph	H	CH_2=$CHCH_2$	H	3	**1d**	99
5	Ph	H	Ph_2CH	H	3	**1e**	99
6	Ph	H	$PhCH_2$	$PhCH_2$	10	**1f**	98
7	Ph	H	$PhCH_2$	Me	10	**1g**	95
8	Ph	H			5	**1h**	98
9	4-Cl-C_6H_4	H	$PhCH_2$	H	5	**1i**	93[c]
10	*E*-PhCH=CH	H	Ph	H	5	**1j**	98
11	*E*-PhCH=CH	H	$PhCH_2$	H	3	**1k**	99
12	*E*-PhCH=CH	H	$PhCH_2$	$PhCH_2$	12	**1l**	90
13	(*E*)-C_5H_{11}CH=CH	H	$PhCH_2$	H	5	**1m**	95
14	$(CH_3)_2CH$	H	Ph	H	3	**1n**	99
15	$(CH_3)_2CH$	H	$PhCH_2$	H	3	**1o**	99
16	$(CH_3)_2CH$	H	$PhCH_2$	$PhCH_2$	15	**1p**	74[b,c]
17	$PhCH_2CH_2$	H	$PhCH_2$	H	10	**1q**	98
18	Ph	Me	$PhCH_2$	H	35	**1r**	21[b,c,d]
19	CH_2=CH	Me	$PhCH_2$	H	20	**1s**	–
20	PhCH=CH	Me	$PhCH_2$	H	20	**1t**	2[bcd]
21	CH_3CH_2	CH_3CH_2	$PhCH_2$	H	18	**1u**	77[b,c,d]
22			$PhCH_2$	H	13	**1v**	98[b,d]
23			$PhCH_2$	H	12	**1w**[e]	97
24			$PhCH_2$	H	9	**1x**	99 [b,d]
25			$PhCH_2$	H	11	**1y**	98 [b,c,d]

[a] Isolated crude pure compounds (>92% purity by ^{1}H NMR). [b] Carbonyl compound and amine were allowed to react during 5 min before TMSCN addition. [c] The corresponding cyanohydrin was the other product obtained. [d] 1.3 and 1.2 equiv. of amine and TMSCN were added, respectively. [e] Obtained as a >95/5 *cis/trans* mixture of diastereomers.